Conferences and Reviews

Drug Dosing Guidelines in Patients With Renal Failure

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The metabolism and excretion of many drugs and their pharmacologically active metabolites depend on normal renal function. Accumulation and toxicity can develop rapidly if dosages are not adjusted in patients with impaired renal function. In addition, many drugs that are not dependent on the kidneys for elimination may exert untoward effects in the uremic milieu of advanced renal disease. A familiarity with basic pharmacologic principles and a systematic approach are necessary when adjusting drug dosages in patients with abnormal kidney function. The distinct steps involve calculating the patient's glomerular filtration rate, choosing and administering a loading dose, determining a maintenance dose, and a decision regarding monitoring of drug concentrations. If done properly, therapy in renal patients should achieve the desired pharmacologic effects while avoiding drug toxicity. Physicians must not oversimplify the pharmacologic complexities presented by patients with renal failure by relying excessively on nomograms and "cookbook" equations. In addition to a reduced glomerular filtration rate, patients with renal disease often have alterations in pharmacokinetics such as bioavailability, protein binding, hepatic biotransformation, and volume of distribution. An awareness of biologically active or toxic metabolites of parent compounds that accumulate when the glomerular filtration rate is reduced is also necessary to avoid toxicity. The effects of dialysis on drug elimination and the need for supplemental dosing are additional considerations in patients undergoing renal replacement therapy.

(Swan SK, Bennett WM: Drug dosing guidelines in patients with renal failure. West J Med 1992 Jun; 156:633-638)

Drug elimination by the kidneys correlates with the glomerular filtration rate. It is thus logical to use this measurement for adjusting dosages in patients with renal failure. Other pharmacokinetic variables, however, may be altered in patients with renal insufficiency, including drug absorption, volume of distribution, degree of protein binding, and biotransformation. Hence, dosage adjustments cannot be based solely on decreased renal excretory rates.

Absorption rates of many therapeutic agents may be reduced by azotemia-associated vomiting or sluggish gut motility due to uremic neuropathy, the use of phosphate binders, or both. Aluminum-containing binders may form insoluble compounds with certain drugs such as tetracycline or ferrous sulfate and block absorption. Bowel wall edema in a patient with hypoalbuminemia may also diminish drug absorption.

The volume of distribution for a specific drug is derived by dividing the total amount of drug in the body by its plasma concentration. It does not refer to a specific anatomic compartment per se; instead, it is used mathematically to determine the dose of a drug necessary to achieve a desired plasma concentration. The volume of distribution for a specific drug may be altered in patients with uremia, specifically by alterations in the extracellular fluid volume state. For example, volume contraction tends to decrease and edema and ascites increase the volume of distribution for hydrophilic and highly protein-bound agents. Conversely, digoxin, methotrexate, and insulin have decreased distribution volumes in the uremic state. As a general rule, plasma concentrations of a drug correlate inversely with its volume of distribution.

Protein binding is often altered in the uremic state and can affect the volume of distribution and the proportion of free or biologically active drug available. Specifically, protein binding of acidic drugs (Table 1) is diminished in uremic patients due to a displacement by organic acid accumulation and structural alterations in albumin. For example, penicillins and phenytoin, which are normally highly protein-bound, are displaced from albumin by organic acids that accumulate in patients with uremia, leading to increased levels of free or "active" drug. Conversely, higher concentrations of unbound drug are available for enzymatic metabolism in the liver, which may lead to increased drug clearance rates, particularly if drug metabolites are excreted by nonrenal routes.

TABLE 1.—*Acidic Compounds With Decreased Protein Binding in Uremia*

Barbiturates	Phenytoin
Cephalosporins	Salicylate
Clofibrate	Sulfonamide
Diazoxide	Valproate
Furosemide	Warfarin
Penicillins	

Biotransformation may also be altered by renal insufficiency. Hepatic oxidative pathways for certain drugs (phenytoin, propranolol) may be accelerated, and other metabolic functions such as acetylation, hydrolysis, and reduction may be slowed. Active or toxic metabolites of parent compounds may accumulate in patients with renal failure. The antiarrhythmic agent procainamide is metabolized to *N*-acetyl-procainamide, which is excreted by the kidneys. Thus, the antiarrhythmic properties and toxicity of procainamide and its active metabolite are additive, especially in patients with renal failure. A commonly used narcotic, meperidine, is biotransformed to normeperidine, which undergoes renal excretion. Although this metabolite has little narcotic effect, it lowers the seizure threshold as it accumulates in uremic pa-

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tients. Similarly, active metabolites of benzodiazepines can accumulate in patients with impaired renal function, resulting in prolonged sedation.

Thus, pharmacologic considerations in patients with renal impairment demand an appreciation of altered pharmacokinetic principles in this patient population. Detailed pharmacokinetic information with extensive reference material is beyond the scope of this discussion and can be found elsewhere.

Dosimetry in Renal Failure

The following outline provides a stepwise approach to assist physicians in prescribing drug therapy for patients with renal failure. Again, it must be emphasized that these steps simply provide a framework for dosage adjustments in patients with renal impairment and must be modified on a case-by-case basis.

Initial Assessment

A history and physical examination constitute the first step in assessing dosimetry in patients with renal impairment. Specifically, renal dysfunction should be defined as acute or chronic and the cause ascertained if possible. In addition, a history of previous drug intolerance or toxicity should be determined. The patient's current medication list (both prescription and nonprescription formulations) must likewise be examined to identify possible adverse drug interactions and nephrotoxins. The physical examination will provide height and body weight information that may be necessary, for example, in an obese patient to calculate ideal body weight. For men, the ideal body weight is 50 kg plus 2.3 kg for each 2.5 cm over 152 cm. For women, the formulation is 45.5 kg plus 2.3 kg per 2.5 cm over 152 cm. An assessment of the extracellular fluid volume is also key because alterations in this measurement can affect the distribution volumes of many pharmacologic agents. The identification of extrarenal disease—hepatic dysfunction—may lead to the need for even greater dosage adjustments, depending on the pharmacologic agents administered.

Calculate Creatinine Clearance

The rate of drug elimination by the kidneys is proportional to the glomerular filtration rate. It is important to remember that serum creatinine and blood urea nitrogen levels are crude and often inaccurate measures of renal function. Thus, creatinine clearance (C_{cr}) is more accurately used to approximate the glomerular filtration rate. Because body mass and age affect serum creatinine concentrations and clearance, C_{cr} can be estimated by the Cockcroft and Gault equation[1]:

$$C_{cr} = \frac{(140 - \text{age})(\text{body weight in kg})}{72 \times \text{serum creatinine}}$$

In women, this result should be multiplied by 0.85. Remember that this equation represents only an approximation of the glomerular filtration rate even if accurately done. Specifically, the serum creatinine level does not reflect the C_{cr} in patients with rapidly changing renal function. In acute renal dysfunction, timed urine collections should be done and mid-collection serum creatinine values used to calculate the C_{cr}. Both the calculated and endogenous forms of C_{cr} overestimate the inulin clearance, the conventional "gold standard" in glomerular filtration determination.[2] Nevertheless, the C_{cr} is an approximation useful in clinical dosimetry.

Choose a Loading Dose

In many cases, a rapid achievement of therapeutic drug concentrations is the pharmacologic goal. If several doses of a drug are administered at uniform intervals, steady-state drug concentrations are achieved after 3.3 drug-elimination half-lives. Because the half-life may be greatly prolonged in renal failure, effective therapy may be greatly delayed if maintenance doses are adjusted to reflect the renal failure elimination half-life. Thus, a standard loading dose, practically speaking, should be administered to patients with renal failure to reach therapeutic drug levels rapidly. The loading dose can be calculated by the following formula where *Vd* is the volume of distribution (liters per kg), IBW is the ideal body weight (kg), and *Cp* is the desired plasma concentration (mg per liter):

$$\text{Loading dose} = Vd \times \text{IBW} \times Cp$$

As discussed previously, if extracellular volume depletion exists, the volume of distribution may be reduced for certain pharmacologic agents, and slight reductions in the loading dose would be prudent. Specifically, drugs with narrow therapeutic:toxic profiles such as digoxin and ototoxic aminoglycosides should be administered with a 25% reduction in their loading dose when volume contraction is present.

Choose a Maintenance Dose

Deriving a maintenance dose for a drug ensures steady-state blood concentrations and diminishes the likelihood of subtherapeutic regimens or toxicity. If the clinical need for drug action is not urgent, maintenance doses can be used from the initiation of therapy to gradually achieve steady-state concentrations without the need for a loading dose. Adjustments in maintenance doses for patients with renal insufficiency can be accomplished by one of two methods or a combination of the two. The "interval extension" method involves lengthening the time period between individual doses of a drug that corresponds to the degree of delayed drug excretion and reflects the extent of renal impairment. This method is particularly useful for drugs with a wide therapeutic range and long half-life. It can, however, result in periods of subtherapeutic drug levels between doses and should be used judiciously. Another alternative, the "dosage reduction" method, involves reducing the absolute amount of drug administered at each dosing interval proportional to the patient's degree of renal failure. The dosing interval remains unchanged in this setting, and more constant drug concentrations are generally achieved. It risks greater toxicity, however, because the difference between peak and trough levels is minimized and trough levels tend to be higher. Thus, combining these two approaches often becomes necessary to provide effective therapy for patients with renal dysfunction while minimizing toxicity. Recommendations for maintenance dosage adjustments have been published elsewhere,[3] and a limited number of clinically relevant examples are tabulated in Table 2. Again, these recommendations provide only a general guideline for dosing adjustments and must be adapted to a specific patient's situation.

Monitoring Drug Levels

Varying the dose or dosing interval for a given therapeutic agent may not be sufficient to guarantee therapeutic efficacy and avoid toxicity in patients with renal failure. If a prescrib-

TABLE 2.—*Dosage Adjustments for Patients With Renal Failure*

Drug, Toxicity, and Notes	Elimination and Metabolism	Half-life (Normal/ ESRD), hours	Plasma Protein Binding, %	Volume of Distribution, liters/kg	Method*	Adjustment for Renal Failure GFR, ml/min		Supplement for Dialysis
						10-50	< 10	
ANTIMICROBIAL AGENTS								
Aminoglycoside Antibiotics *Ototoxic, nephrotoxic; rare respiratory paralysis; serum levels to ensure efficacy. Posthemodialysis dose is ⅔ of normal maintenance dose or ½ of a loading dose; 50% to 90% absorbed from peritoneum; volume of distribution larger with obesity, edema, or ascites*								
Gentamicin sulfate *Concurrent use of penicillins may result in subtherapeutic blood levels*	Renal	1.7-2/20-60	<5	0.23-0.26	D, I	30-70 every 12	20-30 every 24-48	Yes (He, PD)
Netilmicin sulfate	Renal	2.2-2.7/35-72	<5	0.16-0.30	D, I	20-60 every 12	10-20 every 24-48	Yes (He, PD)
Tobramycin *Concurrent use of penicillins may result in subtherapeutic blood levels*	Renal	2.5/27-60	<5	0.22-0.33	D, I	30-70 every 12	20-30 every 24-48	Yes (He, PD)
Cephalosporin Antibiotics *Rare allergic interstitial nephritis; absorbed well when administered intraperitoneally, may cause bleeding in patients with renal failure*								
Cefamandole nafate	Renal	1/6-11	75	0.16-0.25	I	6-8	12	Yes (He, PD)
Cefazolin sodium	Renal	1.8-2/40-70	80	0.13-0.22	I	12	24-48	Yes (He, PD)
Cefodizime	Renal	2.5-4/7.4	80-90	0.13-0.2	D	50-100	50	No (He, PD)
Cefoxitin sodium *May raise creatinine levels by interfering with assay*	Renal	1/13-23	41-75	0.13-0.39	I	8-12	24-48	Yes (He, PD) No (PD)
Ceftazidime	Renal	1.2/13-25	17	0.28-0.4	I	24-48	48-72	Yes (He, PD)
Ceftriaxone sodium *Monitor levels in dialysis patients*	Renal (hepatic)	7-9/12-24	85-95	0.12-0.14	I	Unchanged	24	No (He, PD)
Cefuroxime	Renal	1.1-1.4/17	33	0.13-1.8	I	8-12	24	Yes (He)
Cephalothin sodium	Renal	0.5-1/3-18	65	0.26	I	6-8	12	Yes (He)
Miscellaneous Antibacterial Antibiotics								
Aztreonam	Renal	1.7-2.9/6-8	50-60	0.1-0.2	D	50-75	25	Yes (He, PD)
Chloramphenicol *t-½ Markedly prolonged with combined liver and kidney dysfunction*	Hepatic	1.6-3.3/3.7	60	0.6-1.0	--	Unchanged	Unchanged	No (He, PD)
Ciprofloxacin *Poorly absorbed with the use of antacids or phosphate binders*	Hepatic	3-6/6-9	20-40	2.1	D	50	33	Yes (He, PD)
Clindamycin HCl	Hepatic	2-4/3-5	60-95	0.6-1.2	--	Unchanged	Unchanged	No (He, PD)
Erythromycin *Ototoxic in high doses in patients with ESRD*	Hepatic	1.4/5-6	60-95	0.8	D	Unchanged	50-75	No (He, PD)
Fleroxacin	Renal (hepatic)	9-12/17-25	<30	>1.5	D	50-100	50	No (He, PD)
Imipenem	Renal	1/4	13-21	0.30	D	50	25	Yes (He)
Lomefloxacin HCl	Renal	7-8/38-44	15	2.2-2.5	D	50-100	50	No (He, PD)
Metronidazole	Hepatic	6-14/21	20	0.25-0.85	D	Unchanged	50	Yes (He)
Norfloxacin	Hepatic	3.5-6.5/8	14	<0.5	I	12-24	Avoid	No (He)
Spectinomycin HCl	Renal	1.6/16-29	5-20	0.25	--	Unchanged	Unchanged	No (He, PD)
Sulfadiazine	Renal	8-17	22-34/30-55	?	D I	25-50 8-24	Avoid 48-72	?
Sulfamethoxazole	Renal	9-11/20-50	40-60	0.28-0.38	I	18	24	Yes (He)
Trimethoprim *Has antifolate activity*	Renal	9-13/20-49	30-70	1-2.2	I	18	24	Yes (He)
Vancomycin HCl *Ototoxic at serum levels > 50 mg/ml, 40% to 70% absorbed from peritoneum*	Renal	6-8/200-250	10-50	0.47-0.84	I	72-240	240	No (He, PD)

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Drug, Toxicity, and Notes	Elimination and Metabolism	Half-life (Normal/ESRD), hours	Plasma Protein Binding, %	Volume of Distribution, liters/kg	Method*	Adjustment for Renal Failure GFR, ml/min 10-50	Adjustment for Renal Failure GFR, ml/min < 10	Supplement for Dialysis
Penicillins								
Agents in this group cause allergic interstitial nephritis; seizures and coagulopathy occur at high blood levels								
Amoxicillin	Renal	0.9-2.3/5-20	15-25	0.26	I	6-12	12-16	Yes (He)
Ampicillin *Contains 3 mEq Na^+/gram*	Renal	0.8-1.5/7-20	8-20	0.17-0.31	I	6-12	12-16	Yes (He) No (PD)
Dicloxacillin sodium	Renal	0.7/1-2	91-98	0.13-0.19	--	Unchanged	Unchanged	No (He, PD)
Mezlocillin sodium *Contains 1.9 mEq Na^+/gram*	Renal	0.6-1.2/2.6-5.4	20-46	0.17-0.20	I	6-8	8	No (He, PD)
Nafcillin sodium *Causes coagulopathy*	Hepatic	0.5/1.2	80-90	0.31-0.38	--	Unchanged	Unchanged	No (He, PD)
Penicillin G *Potassium salt has 1.7 mEq/million units; causes convulsions, false-positive urine protein reactions*	Renal	0.5/6-20	40-60	0.3-0.42	D	75	25-50	Yes (He)
Piperacillin sodium *Contains 1.9 mEq Na^+/gram*	Renal	0.8-1.5/3.3-5.1	20-40	0.18-0.30	I	6-8	8	Yes (He)
Ticarcillin disodium *Contains 5.2 mEq Na^+/gram*	Renal	1.2/16	45-60	0.14-0.21	D, I	1-2 grams every 8 h	1 gram every 12 h	Yes (He) No (PD)
Tetracycline Antibiotics								
Agents in this group potentiate acidosis, raise blood urea nitrogen and phosphorus levels, and increase catabolism; their use should be avoided in renal failure								
Doxycycline *Group drug of choice for extrarenal infection*	Hepatic	15-24/18-25	80-93	0.75	--	Unchanged	Unchanged	No (He, PD)
Antifungal Antibiotics								
Amphotericin B *Nephrotoxic; causes renal tubular acidosis, hypokalemia, and nephrogenic diabetes insipidus*	Nonrenal	24/24	90	4	I	24	24-36	No (He, PD)
Fluconazole *May increase blood cyclosporine levels*	Renal	22-36/98	11	0.5-0.6	I	24-48	48-72	Yes (He)
Flucytosine *Causes hepatic dysfunction and marrow suppression is more common in azotemic patients*	Renal	3-6/75-200	< 10	0.6	I	12-24	24-48	Yes (He, PD)
Ketoconazole	Hepatic	1.5-3.3/3.3	99	1.9-3.6	--	Unchanged	Unchanged	No (He, PD)
Antimycobacterial Antibiotics								
Clofazimine	Nonrenal	70 d/70 d	Low	High	--	Unchanged	Unchanged	No (He, PD)
Ethambutol HCl *Causes decreased vision acuity and peripheral neuritis*	Renal	4/7-15	10-30	1.6-2.3	I	24-36	48	Yes (He)
Isoniazid	Hepatic	0.7-4/8-17	< 10	0.6	D	Unchanged	50	Yes (He)
Pyrazinamide	Hepatic	9.5/9.5	50	0.7	D	Unchanged	Avoid	Avoid
Rifampin *May cause acute renal failure, potassium wasting, and renal tubular defects; biologically active metabolite, desacetyl-rifampicin*	Hepatic	1.5-5/1.8-11	60-90	0.9	--	Unchanged	Unchanged	No (He)
Antiviral Antibiotics								
Acyclovir *Neurotoxic in patients with renal failure; may cause acute renal failure if rapidly administered intravenously*	Hepatic (renal)	2.1-3.8/20	15-30	0.6-0.8	D, I	5 mg/kg every 12-24 h	2.5 mg/kg every 24 h	Yes (He)
Amantadine HCl	Renal	12/500	60	4-5	I	48-72	168	No (He, PD)
2′,3′-Dideoxycytidine (ddC)	Renal	0.5-2.2/Prolonged	?	0.54-0.6	D	50-75	25-50	?
2′,3′-Dideoxyinosine (ddI)	Hepatic (renal)	0.5-4.64/Prolonged	< 5	1	D	75-100	50-75	?
Foscarnet sodium	Renal	36-72/Prolonged	?	1-1.7	D	15-50	Avoid	Yes (He)
ANTIHYPERTENSIVE AGENTS								
In this group, blood pressure is best guide to dose and interval								

Adrenergic Modulators								
Clonidine *Rebound hypertension occurs if drug is abruptly withdrawn; tricyclic antidepressants decrease efficacy; potentiates central nervous system depressant effects of alcohol, sedatives*	Hepatic (renal)	6-23/39-42	20-40	3-6	--	Unchanged	Unchanged	No (He, PD)
Methyldopa *Causes orthostatic hypotension; retroperitoneal fibrosis; prolonged hypotension due to retained active metabolites; interferes with serum creatinine measurement*	Renal (hepatic)	1.5-6/6-16	<15	0.5	I	8-12	12-24	Yes (He)
Prazosin HCl *Profound hypotension may occur with first dose*	Hepatic	2-3/2-3	97	1.2-1.7	--	Unchanged	Unchanged	No (He, PD)
Angiotensin-converting Enzyme Inhibitors *Hypotensive effect magnified by natriuretic agents or sodium depletion; hyperkalemia; acute renal dysfunction with bilateral or transplant renal artery stenosis; dry cough occurs in 5% to 10% of patients*								
Benazepril HCl	Renal (hepatic)	21-22/Prolonged	>95	0.09-0.16	D	25-100	25-50	No (He)
Captopril *Causes rare proteinuria, nephrotic syndrome; dysgeusia, granulocytopenia; can increase serum digoxin levels*	Renal (hepatic)	1.9/21-32	25-30	0.7-3	D, I	75 every 12-18 h	50 every 24 h	Yes (He)
Cilazapril	Renal (hepatic)	7.5/8.2	?	0.29-0.36	D	25-100	25-50	Yes (He)
Enalapril maleate *Enalaprilat is the active moiety formed in liver*	Renal (hepatic)	11-24/40-60	50-60	?	D	75-100	50	Yes (He)
Lisinopril	Renal	12.6/40-50	<10	1.3-1.5	D	50-75	25-50	Yes (He)
β-Blockers								
Atenolol *Significant accumulation in patients with ESRD*	Renal	6-9/15-35	<5	1.1	D, I	50 every 48 h	50 every 96 h	Yes (He)
Betaxolol HCl	Hepatic	14-22/31.2	55	4.9-9.8	D	Unchanged	50	No (He, PD)
Labetalol HCl	Hepatic	3-8/3-8	50	5.6	--	Unchanged	Unchanged	No (He, PD)
Metoprolol tartrate	Hepatic	2.5-4.5/2.5-4.5	8	5-6	--	Unchanged	Unchanged	Yes (He)
Propranolol HCl *Metabolites may accumulate; increases bilirubin level by assay interference; less frequent doses in some patients with ESRD; hypoglycemia reported in ESRD*	Hepatic	2-6/1-6	90-96	3-4	--	Unchanged	Unchanged	No (He)
Calcium Blocking Agents *Headache, flushing, and dizziness in patients with renal disease; may increase serum digoxin and cyclosporine levels*								
Diltiazem HCl *Active metabolites; acute renal dysfunction reported*	Hepatic	2-8/3.5	98	3-5	--	Unchanged	Unchanged	No (He, PD)
Isradipine	Hepatic	1.9-4.8/10	?	3-4	--	Unchanged	Unchanged	No (He, PD)
Nifedipine *Active metabolites; edema; acute renal dysfunction reported*	Hepatic	4-5.5/5-7	92-98	1.4	--	Unchanged	Unchanged	No (He, PD)
Nisoldipine	Hepatic	6.6-8/6.8-10	99	2.3-7.1	--	Unchanged	Unchanged	No (He, PD)
Verapamil HCl *Active metabolites; acute renal dysfunction reported*	Hepatic	3-7/2.4-4	83-93	3-6	--	Unchanged	Unchanged	No (He, PD)
Cardiac Glycosides *Add to uremic gastrointestinal symptoms; serum levels guide therapy; toxicity enhanced by dialysis potassium and magnesium removal*								
Digitoxin *Protein binding is decreased by dialysis; volume of distribution reduced by uremia*	Hepatic (renal)	144-200/210	94	0.6	D	Unchanged	50-75	No (He, PD)
Digoxin *Radioimmunoassay may overestimate serum levels in uremia; clearance reduced by spironolactone, quinidine, verapamil; hypokalemia, hypomagnesemia enhance toxicity; volume of distribution decreased in ESRD; serum level 12 hours after first dose is best guide in ESRD*	Renal (Nonrenal 15%-40%)	36-44/80-120	20-30	5-8	D, I	25-75 every 36 h	10-25 every 48 h	No (He, PD)

ESRD = end-stage renal disease, GFR = glomerular filtration rate, HCl = hydrochloride, He = hemodialysis, PD = peritoneal dialysis

ing physician knows the therapeutic drug concentration desired and which levels are considered toxic, drug level monitoring can greatly enhance individualized therapy, especially in patients with renal failure. Drug concentrations are commonly determined from serum specimens, but occasionally plasma or whole blood concentrations are required. Interpreting drug concentrations requires a knowledge of the exact dose given, the route of drug administration, the elapsed time from the last dose, and the drug's elimination half-life in a specific patient. Drug concentrations may be used after an appropriate loading dose or three to four maintenance doses have been administered to assure that steady-state concentrations have been achieved. Peak levels reflect the highest drug concentration achieved after an initial rapid distribution phase and are measured 30 to 60 minutes after parenteral administration or one to two hours after oral ingestion. Peak values tend to correlate with drug efficacy. Trough levels, on the other hand, should be measured immediately before the next dose to indicate the lowest concentration of drug in the body and thus systemic clearance. Drug trough values tend to be used as indicators of toxicity.

The interpretation of drug levels must include clinical evaluation because toxicity can occur with levels within the "therapeutic" range. For example, digitalis intoxication can occur in the presence of therapeutic serum levels if hypokalemia or metabolic alkalosis coexists. An increase in the unbound or biologically active fraction of a given drug may not be reflected in drug level monitoring because most assays measure total drug concentration (protein-bound plus unbound fractions). This point is illustrated by phenytoin, which is highly protein-bound under normal circumstances. In hypoalbuminemic patients such as those with the nephrotic syndrome or in uremic states, the protein-bound fraction of phenytoin is substantially reduced but the unbound or biologically active fraction is increased. In addition, the increased free form of phenytoin leads to increased hepatic metabolism. Thus, it is prudent to measure free phenytoin concentrations in uremic or hypoalbuminemic patients because "therapeutic" levels of total drug might mask toxic or subtherapeutic levels of unbound drug.

Dialysis and Drug Dosing

Patients undergoing dialysis treatment require special attention with regard to dose scheduling and the possible need for supplemental dosing for agents substantially cleared by dialysis. Factors affecting dialysis drug clearance are listed in Table 3. The molecular weight, water solubility, and degree of protein binding for any given drug represent the major determinants of its dialyzability. The smaller (less than 500 daltons), the more hydrophilic, and the less protein-bound a compound is, the greater the clearance by dialysis treatments. Continuous hemofiltration methods are becoming increasingly common in intensive care units, and an awareness of drug removal by these procedures is essential. Solutes and pharmacologic agents are removed by convective transport in hemofiltration procedures. Thus, any compound distributed in plasma water and not highly protein-bound will cross hemofiltration membranes, appearing in the ultrafiltrate. When the filtrate generated by hemofiltration is adequate to correct uremia and a drug is less than 60% protein-bound, sufficient drug removal will be likely and supplemental dosing warranted.

In summary, responses to drug therapy in patients with renal failure are markedly heterogeneous and require thoughtful consideration and ongoing evaluation by prescribing physicians. Although reductions in glomerular filtration rates can be factored mathematically into dosage-adjustment strategies, this merely represents the initial step and one of many pharmacokinetic and metabolic principles to be considered. Dosing information such as that provided in Table 2 must be applied to individual patients in a prudent manner, taking into account specific alterations in drug handling induced by the degree of renal impairment and any other concurrent conditions.

TABLE 3.—*Factors Affecting Dialysis Drug Clearance*

Drug properties
Molecular weight
Charge
Water solubility
Volume of distribution
Dialyzer membrane binding
Erythrocyte partitioning
Nonrenal excretory pathways
Membrane properties
Blood flow
Pore size
Vascular disease (peritoneal dialysis)
Surface area
Fluid films
Loculation/sclerosis (peritoneal dialysis)
Dialysate properties
Flow rate
Solute composition
Volume (peritoneal dialysis)
Temperature
pH
Miscellaneous
Convective transport during ultrafiltration

Suggested Reading

Aronoff GR, Abel SR: Principles of administering drugs to patients with renal failure, *In* Bennett WM, McCarron DA, Brenner BM, Stein JH (Eds): Pharmacotherapy of Renal Disease and Hypertension. New York, NY, Churchill Livingstone, 1987, pp 1-19

Brater DC: Pocket Manual of Drug Use in Clinical Medicine. Philadelphia, Pa, BC Decker, 1987

Turnheim K: Pitfalls of pharmacokinetic dosage guidelines in renal insufficiency. Eur J Clin Pharmacol 1991; 40:87-93

REFERENCES

1. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41

2. Bennett WM, Porter GA: Endogenous creatinine clearance as a clinical measure of glomerular filtration rate. Br Med J 1971; 4:83-86

3. Bennett WM, Aronoff GR, Golper TA, Morrison G, Singer I, Brater DC: Drug Prescribing in Renal Failure: Dosing Guidelines for Adults, 2nd Ed. Philadelphia, Pa, American College of Physicians, 1991